REMARKS

Claims 22-33 and 49-92 are pending in the subject application. Claims - have been amended. The amendments to claims -- is supported by the specification as filed, and no new matter is presented. Favorable reconsideration in light of the remarks which follow is respectfully requested.

1. 35 U.S.C §112 Rejections

Claims 22-33 have been rejected under 35 U.S.C.§112, second paragraph, as being indefinite. In particular, the Office asserts:

> It is unclear as to what applicant intends to convey by 'if there is a solubilizing point' in claim 22 (step e); if there is a solvent, then won't there be a solubilizing point? It is also unclear what the expression 'the reference particles are water' in step f is intended to convey. How can water form particles? The claim steps are very confusing.
>
> The method in the independent claim 22 does not recite a concentration or lyophilization step; yet the dependent claim 33 recites 'a concentrate or lyophilisate'. Therefore, claim 33 is indefinite.

Applicants respectfully traverse. However, to expedite prosecution, Applicants have amended claim 22 for further clarity. In particular, Applicants' claim 22 reads:

> 22. A method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising:
> a. selecting a first amphiphilic lipid component; and
> b. selecting a second amphiphilic lipid component and selecting at least one active ingredient;
> c. said first and second amphiphilic lipid components being selected so that the solubility of the second amphiphilic lipid component in a pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium;
> d. adapting the composition or concentration of the preparation for transport through skin or mucous membrane, by adjusting the content of the more soluble component to less than 0.1 mole percent of its content at which the enveloped droplets solubilize, if there is a solubilizing point; and
> e. adjusting the content of amphiphilic lipid components, such that the ratio of the permeation capability relative to reference particles which are much smaller than the constrictions of the barrier, wherein the reference particles are water molecules, is between 10-5 and 1;
> f. producing a transfersome suspension by means of applying energy to the mixture of said amphiphilic lipid components including at least one active ingredient, said transfersomes comprising liquid droplets

> encompassed within a sheath comprising said amphiphilic lipid components, said amphiphilic lipid components being selected such that said transfersomes are capable of undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized, said active ingredient being contained in said liquid droplets, or in said sheath, or in both said liquid droplets and said sheath.

Regarding the Office's statement that "if there is a solvent, then won't there be a solubilizing point" Applicants respectfully submit that there is no claim to a solvent and that the droplets are not located in a solvent as it appears the Office is asserting. Rather, as clearly set out in the claim, the components are in a pharmaceutically acceptable suspending medium.

In general, the preparations of the present invention are formed by enveloped droplets that enclose an active agent. These droplets are suspended in a pharmaceutically acceptable suspending medium. The droplets are essentially formed of two amphiphilic components which differ in their solubility in the suspending medium by a factor of at least ten. The first component is less soluble than the second and is capable of forming vesicles (droplets) in the medium. The vesicles are in the form of membrane like sheaths which surround the active agent. Applicants found that the first component, alone, forms droplets that are not flexible enough to permeate through barriers (e.g. the skin). Thus, Applicants insert a second component (more soluble than the first component) into the droplet sheath. Insertion of the second component destabilizes the droplets and make them ultradeformable.

Applicants determine how much of the more soluble component to add by the solubilization point of the droplets. If too much of the more soluble component is added and inserted into the droplet sheath, the droplets will not be stable enough and will solubilize. Thus, the solubilization concentration is the concentration at which the more soluble component causes solubilization of the droplets. This concentration must not be reached. However, depending on what the more and less soluble components are, it is also possible that the more soluble component will not be capable of solubilizing the droplet. In this case, no solubilization point can be reached. Thus, step e (amended as step d) indicates a "content at which the enveloped droplets solubilize, if there is a solubilizing point".

Regarding the Office's statement "How can water form particles?" Applicants have amended claim 22 to refer to water molecules.

Regarding the Office's objection to "concentrate or lyophilisate" in claim 33, Applicants have amended claim 33 as required. In particular, claim 33 recites "the method of claim 22, wherein shortly before use, the enveloped droplets are prepared, from a concentrate or lyophilisate, which was prepared from said transfersome suspension." The methods for the preparation of concentrates and lyophilisates being well-known in the art.

2. 35 U.S.C. §102 Rejections

Claims 22-33 and 49-92 have been rejected under 35 U.S.C. §102(b) as anticipated by EP 0 475 160 of record (English equivalent, US 6,165,500). The Office asserts:

> EP discloses instant composition (transfersomes) containing a drug, amphiphilic lipids (such as PC and PG) and a surfactant (oleic acid) in instant amounts and a method of preparation (see the entire document and the English equivalent). The Examples 32-39 show the amounts of the lipids and surfactant which appear to fall within the claimed limits. Although the reference does not explicitly recite the claimed steps such as selecting the lipids, adopting the composition by adjusting the amounts of the soluble component and adjusting the concentration of the lipid, since one cannot come up with specific amounts of the components as seen in example 32-39 of the reference without experimentation, the claimed steps are deemed to be implicit.

Applicants respectfully traverse.

As set out above, the solubilization point is the point at which the more soluble component causes solubilization of the droplets (vesicles). The present preparations form enveloped droplets (vesicles) that enclose an active agent. These droplets are essentially formed of two amphiphilic components (first component = less soluble component; second component = more soluble component). The first component, alone, will form droplets. Applicants insert a second component (more soluble) into the droplet sheath. Insertion of the second component destabilizes the droplets and make them ultradeformable. However, if too much of the second (more soluble)

component is added, then the droplets will solubilize (solubilization concentration). This concentration must not be reached. Thus, Applicants claim a method wherein the second (more soluble) component is added in an amount of less than 0.1 mole percent of its content at which the enveloped droplets solubilize, if there is a solubilizing point. In other words, the second component, if added at a concentration X (concentration X = solubilization concentration), will cause solubilization of the droplets. Applicants add the second component in an amount of less than 0.1X. Thus, the solubilization concentration does not refer to any absolute concentration or ratios of surfactants and lipids, but rather, only relates to the concentration of added more soluble substance at which solubilization of the droplets is reached.

The EP'160 reference describes transfersomes having a content of surface active substance corresponding to 0.1 to 99 mol % of the content of the substance representing the solubilization concentration of the droplets. EP'160, thus, describes transfersomes wherein the amount of surfactant that must be added to render the membrane flexible (and thus the whole vesicle a transfersome) is between 0.1 and 99 mol-% of that amount of surfactant which characterizes the solubilization point. In other words, there is an amount of surfactant (in mol-%), at which the solubilization point occurs. Further, the actual amount of surfactant in the system must be at least 0.1 mol% of this solubilizing amount of surfactant to render the membrane flexible.

Applicants, on the other hand, teach a method wherein the more soluble component is added in an amount of <u>less than 0.1 mol%</u> of the solubilization concentration, if there is a solubilization concentration. Thus, the Applicants teach systems wherein, if there is a solubilization point, the phenomenon of membrane destabilization, which produces transfersomes, surprisingly occurs at very, very low amounts of more soluble component. These amounts are less than 0.1 mol% of the amount of more soluble component which would indeed cause solubilization. Thus, whereas EP'160 teaches systems wherein at least 0.1 to 99 mol% of the solubilization concentration must be added to achieve membrane destabilization, the present invention teaches systems wherein membrane destabilization can be achieved at lesser amounts (less than 0.1 mol%). Thus, with the present invention, you do not near the solubilization point at all, yet you achieve flexibilization of the membrane at amounts

less than 0.1 mol% of the solubilization concentration. With the EP'160 reference, if the presently claimed small amounts are used, membrane flexibilization will not be achieved at all.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

It is clear from the foregoing that the present claims are not anticipated by EP'160. In particular, Applicants teach a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal wherein a more soluble component is added in an amount of less than 0.1 mole percent of its content at which the enveloped droplets solubilize, if there is a solubilizing point. EP'160, on the other hand, describes transfersomes having a content of surface active substance corresponding to 0.1 to 99 mol % of the content of the substance representing the solubilization concentration of the droplets. This is not within Applicants' claimed range.

Further, Applicants' claimed range would not be inherent in EP'160. It is well established that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing

may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); MPEP 2112.

EP'160 specifically requires forth a range that is not within Applicants' claimed range. Thus, Applicants' range would not necessarily result from the description of EP'160 as required for inherency.

Further, regarding the Office's citation to Examples 32-39, Applicants respectfully submit that these examples use amounts of surfactants being approximately 0.01 weight-% of the lipid content. However, this amount has nothing to do with the mole-% of the surfactant with regard to its solubilization concentration as set out in Applicants' claims. Thus, reference to these examples does not remedy the deficiencies pointed out above regarding the EP'160 reference.

Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

3. 35 U.S.C. §103 Rejections

Claims 22-33 and 49-92 have been rejected under 35 U.S.C. §103(a) as being obvious over EP 0 475 160 of record (English equivalent, US 6,165,500). The Office asserts:

> As pointed out above, EP teaches a composition containing a drug, amphiphilic lipids and a surfactant in instant amounts and a method of preparation. It is unclear whether the reference teaches all the instant functional parameters. In case they are different, in the absence of showing the criticality, they are deemed to be parameters manipulatable by an artisan to obtain the best possible results.

Applicants respectfully traverse.

As set out above, EP'160 describes a system wherein the amount of surfactant that must be added to render the membrane flexible, and thus the whole vesicle a transfersome, must be between 0.1 and 99 mol-% of the amount of surfactant which characterizes the solubilization point. In other words, there is an amount of surfactant (in mol-%), at which the solubilization point occurs, and the actual amount

of surfactant in the system must be at least 0.1 mol-% of this solubilizing amount of surfactant to render the membrane flexible.

In the present invention, Applicants teach a systems where there may or may not be a solubilization point. In the case where there is a solubilization point, the phenomenon of membrane destabilization, which produces transfersomes, surprisingly occurs at very, very low amounts of surfactant. These amounts are less than 0.1 mol-% of the amount of surfactant which would indeed cause solubilization. Thus, with the present invention, you do not near the solubilization point at all, yet you achieve flexibilization of the membrane at amounts less than 0.1 mol% of the solubilization concentration. With the EP'160 reference, membrane flexibilization is not even achieved with these small amounts and, thus, larger amounts are required.

Alternatively, the present invention teaches that there is no solubilization point at all and, thus, the more soluble substance is not capable to solubilize the droplet. Accordingly, it does not matter how much surfactant is added, because the system will never be solubilized.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

As set forth above, Applicants teach, in the present invention, a method for producing a preparation wherein the more soluble component is added in an amount of less than 0.1 mol % of the amount of component which would cause solubilization. The EP'160 reference, on the other hand, describes a system wherein the amount of surfactant added must be between 0.1 and 99 mol % of the amount of surfactant

which characterizes the solubilization point. While the present preparations only require very small amounts of more soluble component to achieve flexibilization of the membrane, EP'160 requires greater amounts.

It is clear from the forgoing that EP'160 does not teach or suggest all of Applicants' claim elements. In particular, the EP'160 reference requires the addition of 0.1 to 99 mol% surfactant to cause membrane flexibilization. Applicants', in the present invention, teach a system that is capable of achieving membrane flexibilization by the addition of a more soluble component in an amount that does not near the solubilization concentration.

Further, regarding the Office's assertion that the present parameters are "deemed to be parameters manipulatable by an artisan to obtain the best possible results", Applicants respectfully submit that even if the concentration of the surfactant set out in EP'160 is manipulated to be within Applicants' presently claimed range, Applicants' preparations would still not be obtained. Applicants teach, in the present invention, systems wherein, if there is a solubilization point, the phenomenon of membrane destabilization, which produces transfersomes, surprisingly occurs at very, very low amounts of surfactant. These amounts are less than 0.1 mol% of the amount of surfactant which would indeed cause solubilization. Thus, whereas EP'160 teaches systems wherein at least 0.1 to 99 mol% of the solubilization concentration must be added to achieve membrane destabilization, the present invention teaches systems wherein membrane destabilization can be achieved at lesser amounts less than 0.1 mol%. With the present invention, you do not near the solubilization point at all, yet you achieve flexibilization of the membrane at amounts less than 0.1 mol% of the solubilization concentration. With the EP'160 reference, if these small amounts are used, membrane flexibilization is not achieved at all. Thus, even if EP'160 utilized less than 0.1 mol% of surfactant, membrane flexibilization would not be achieved and, thus, the present invention would not be obtained.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Reconsideration and allowance of claims 22-33 and 49-92 is respectfully requested in view of the foregoing discussion. Further, withdrawal of the restriction requirement is respectfully requested in view of the forgoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

Applicants conditionally petition for an extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

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